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Clinical paper

Early targeted brain COOLing in the cardiac CATHeterisation laboratory following cardiac arrest (COOLCATH)☆,☆☆

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ABSTRACT

Introduction: Trials demonstrate significant clinical benefit in patients receiving therapeutic hypothermia (TH) after cardiac arrest. However, incidence of mortality and morbidity remains high in this patient group. Rapid targeted brain hypothermia induction, together with prompt correction of the underlying cause may improve outcomes in these patients. This study investigates the efficacy of Rhinochill®, an intranasal cooling device over Blanketrol®, a surface cooling device in inducing TH in cardiac arrest patients within the cardiac catheter laboratory.

Methods: 70 patients were randomized to TH induction with either Rhinochill® or Blanketrol®. Primary outcome measures were time to reach tympanic ≤34 °C from randomisation as a surrogate for brain temperature and oesophageal ≤34 °C from randomisation as a measurement of core body temperature. Secondary outcomes included first hour temperature drop, length of stay in intensive care unit, hospital stay, neurological recovery and all-cause mortality at hospital discharge.

Results: There was no difference in time to reach ≤34 °C between Rhinochill® and Blanketrol® (Tympanic ≤34 °C, 75 vs. 107 mins; $p = 0.101$; Oesophageal ≤34 °C, 85 vs. 115 mins; $p = 0.151$). Tympanic temperature dropped significantly with Rhinochill® in the first hour (1.75 vs. 0.94 °C; $p < 0.001$). No difference was detected in any other secondary outcome measures. Catheter laboratory-based TH induction resulted in a survival to hospital discharge of 67.1%.

Conclusion: In this study, Rhinochill® was not found to be more efficient than Blanketrol® for TH induction, although there was a non-significant trend in favour of Rhinochill® that potentially warrants further investigation with a larger trial.

Introduction

Temperature management has been shown to improve clinical outcomes in patients suffering out-of-hospital cardiac arrest [1,2]. Retrospective registry data demonstrated that delays in therapeutic hypothermia (TH) induction increases mortality [3,4]. More recent data from a large randomised trial have shown no difference in outcomes when comparing targeted temperature management (TTM) at 36 or 33 °C, suggesting the possibility that, prevention of fever following cardiac arrest could be an important mechanism by which neurological injury can be prevented [5]. However, in this latest study, delays in initiation of cooling (mean 130 min) and time to reach 34 °C (mean 5 h) could have offset any potential benefit that TTM at 33 °C could offer in comparison to 36 °C [5,6].

Irrespective of whether methods are employed to reduce core body temperature or to prevent systemic pyrexia, the mortality rate and risk of permanent and disabling brain injury remains high in this patient group. In the TTM trial [5], more than 50% patients in both treatment groups died or had poor neurological function at

Abbreviations: TH, Therapeutic hypothermia; PCI, percutaneous intervention; HAC, Heart Attack Centre; TTM, Targeted temperature management; ROSC, return of spontaneous circulation; ICU, intensive care unit; CPC, cerebral performance category; CTC, Cardiothoracic Centre.

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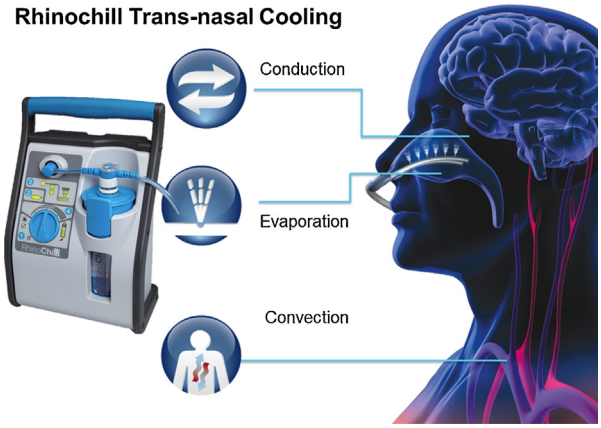

Fig. 1. An illustration of the Rhinochill device and its components.

180 day follow up. The alarming rates of morbidity and mortality associated with cardiac arrest provide a large incentive for research into novel methods of treating this important group of patients.

In practice, several modalities of hypothermia induction exist including cold saline infusion [7], surface blankets [8] and endovascular cooling [9]. Earlier studies indicated that targeted brain cooling is more important in cerebral protection than whole body cooling [10] and associated with lesser side effects [11]. Rhinochill® is a portable, intranasal cooling system that is capable of rapid targeted brain cooling (Fig. 1), as demonstrated in jugular venous temperature recordings in animal models [12]. Thus, it may be able to reduce the risk of neurological injury associated with cardiac arrest [4,10,13]. In addition to its innovative mode of action, its portability allows it to be applied to patients in confined spaces and to be used whilst transferring patients either from the field to the hospital, or between different departments within the hospital.

Coronary artery disease is the most common cause of cardiac arrest [14,15] and it is becoming increasingly common for these patients to be brought directly to heart attack centres (HAC) with cardiac catheter laboratory facilities for emergency percutaneous coronary intervention (PCI). There is strong evidence that an aggressive invasive approach combining emergency PCI and TH in these patients results in better outcomes [16].

In this randomised study, we test the hypothesis that Rhinochill® device is more efficient in TH induction than surface cooling Blanketrol® for cardiac arrest patients presenting to a HAC, in whom an underlying coronary etiology is suspected.

Methods

Study design

Early targeted brain cooling in the cardiac catheterisation laboratory following cardiac arrest (COOLCATH) was designed as a single centre, prospective, open labelled, randomised controlled clinical trial to compare the efficiency of Rhinochill® intranasal cooling device [17] in TH induction to our standard surface-cooling protocol with the Blanketrol® III device [18]. The study received ethical approval from the National Research Ethics Service (Ref: 12/EE/0472). An independent data and safety monitoring committee reviewed the data and performed a comprehensive interim analysis. An independent data monitor performed regular data checks to ensure accuracy and completeness of data collection and strict adherence to the study protocol.

Patients

74 adult patients suffering cardiac arrest, irrespective of any specific initial presenting heart rhythm with return of spontaneous circulation (ROSC) after resuscitation were enrolled between January 2013 and November 2014. The main exclusion criteria were cardiac arrest caused by trauma, head injury, massive haemorrhage, patients without a definitive airway and patients who were already hypothermic on arrival (< 34 °C) (Appendix 1.1). As eligible patients were unconscious on admission, initial written informed consent was obtained from a legal surrogate in accordance with the Helsinki declaration [19]. However, if the patient made sufficient neurological recovery and demonstrated mental capacity, a further informed consent was obtained from the patient.

Randomisation

Patients were admitted directly to the HAC by the ambulance crew, bypassing the local emergency department for emergency catheter laboratory-based diagnostics and therapies. Patients fulfilling the selection criteria were enrolled and randomised (by allocation of a random-sealed envelope) in the cardiac catheter laboratory to receive TH induction by either Rhinochill® or Blanketrol® III cooling blanket in a 1:1 manner. Randomisation was pre-performed by the local research and development office using a computer-generated assignment sequence dictating envelope allocation.

Trial intervention

Baseline tympanic temperatures were recorded immediately after randomisation as a surrogate for brain temperature and an oesophageal temperature probe inserted at the earliest opportunity to measure core body temperature in both treatment arms. The oesophageal temperature recordings were taken to investigate if there was simultaneous drop in core body temperature. Both tympanic and oesophageal temperatures were measured during TH induction every 10 min up to 5 h. It was not in our study protocol to administer any additional TH-inducing agent and therefore, no cold intravenous saline was given to patients in either group.

Rhinochill® 17

The RhinoChill® is the only CE-marked intranasal evaporative cooling system [20] that is capable of inducing TH in cardiac arrest patients. In patients randomised to the Rhinochill® group, TH was initiated in the cardiac catheter laboratory by advancing the intranasal cannulae into each nostril, and switching on the Rhinochill® device to deliver cold vapour into the nasal cavity. The cooling continued throughout the initial induction period, during PCI if performed, and patient transfer to the intensive care unit (ICU), where maintenance cooling by conventional Blanketrol® III could be commenced and Rhinochill® discontinued when the core temperature reached ≤ 34 °C.

Blanketrol® cooling system [18]

Patients allocated to Blanketrol® arm received TH induction in the catheter laboratory by application of surface cooling blankets covering the whole body but sparing a small area in the femoral region to allow arterial access if needed for coronary intervention. Unlike the Rhinochill® device, the Blanketrol® cooling machine needed to be switched off during patient transfer from the catheter laboratory to the ICU.

Table 1
Baseline Characteristics of patients in each group before trial intervention Values are presented as mean (standard deviation) and *n* (%); $p > 0.05$ for all comparisons.

	Blanketrol	Rhinochill
Age–mean (SD)	62.1 (12.5)	63.5 (12.3)
Male sex–*n* (%)	26 (74.3)	30 (85.7)
Body Surface Area–mean (SD) in m^2	1.93 (0.29)	2.03 (0.22)
Cardiac History–*n* (%)	9 (25.7)	16 (45.7)
Bystander CPR–*n* (%)	22 (62.9)	24 (68.6)
Ventricular fibrillation–*n* (%)	33 (94.3)	32 (91.4)
Time of untreated cardiac arrest–mean (SD) in mins	5.06 (11.7)	2.83 (4.7)
Recurrence of cardiac arrest–*n* (%)	13 (37.1)	16 (45.7)
Shocks–mean (SD)	2.89 (2.23)	3.88 (4.56)
Median Time to ROSC from cardiac arrest in mins (IQR)	21 (15–35)	20 (10–36)
Percutaneous intervention–*n* (%)	24 (68.6)	19 (54.3)
Inotropes–*n* (%)	12 (34.3)	10 (28.6)
Intra-aortic balloon pump–*n* (%)	12 (34.3)	12 (34.3)
Mean 1st Tympanic temperature (°C)	35.3 (0.80)	35.3 (1.0)
Mean 1st Oesophageal temperature (°C)	35.3 (0.70)	35.1 (1.0)

General patient management

Patients in both intervention arms were maintained at <34 °C for 24 h with active sedation and protected airway management. The trust protocol for active sedation (Propofol infusion at 0.3–4.0 mg/kg/hr, Morphine Sulphate infusion at 1–2 mg/hr) and shiver prevention (Atracurium at 5 mg/hr) was followed for all enrolled patients. After the maintenance phase (24 h), patients were gradually rewarmed to 36 °C in hourly increments of 0.25–0.5 °C and sedation weaned to allow the patients to regain consciousness. If patients were in cardiogenic shock, intra-aortic balloon pumps were inserted at the discretion of the treating physician in the cardiac catheter laboratory and inotropes infusion was administered in the ICU (Table 1).

Outcome measures

Primary outcomes

Primary outcome measures were time to reach tympanic ≤34 °C from randomisation as a surrogate for brain temperature and oesophageal ≤34 °C from randomisation as a measurement of core body temperature.

Secondary outcomes

Secondary outcomes included rate of cooling in the first hour, length of stay in ICU, hospital stay, neurological recovery and all-cause mortality at hospital discharge. The neurological assessment was made using the cerebral performance category (CPC) scale [21]. The CPC scale ranges from 1 to 5, with 1 indicating an excellent recovery and 5 signifying brain death (Appendix 1.2).

Adverse events were reported and documented as either related to the study intervention or related to the presenting medical condition by the safety monitoring committee. Decisions relating to patient care, other than the method of TH induction, such as withdrawal of active treatment, were taken at the discretion of the treating physician, who was blinded to the trial intervention. Initial temperature data collection and progress of patients' health were monitored daily by the research team, who were not blinded due to the nature of the study intervention. If patients were discharged from hospital within 30 days, then a telephone call was made to ascertain the patient's status.

Statistics

Statistical analysis was conducted in a modified intention to treat population, defined as all randomly assigned patients excluding those withdrawn from the study due to a delayed diagnosis or meeting one of the exclusion criteria. Descriptive statistics are presented for continuous, as well as categorical variables as mean (standard deviation) and tabulated by treatment. Analyses were performed using the computer program R [22]. The time taken to reach target temperature (≤34 °C), duration of ventilation hours, ICU stay and hospital stay were expected to have a non-normal distribution and so the means for the two groups were compared using a two-sample permutation *t*-test with bootstrap 95% confidence limits for the difference between the means. The CPC between the two groups were described in a contingency table and compared using Fisher's exact test. For statistical significance, a *p*-value of 0.05 was adopted. The analysis was performed by an independent statistician.

Results

Patients

A total of 120 cardiac arrest patients were screened for enrolment, out of which 46 patients were excluded for not meeting selection criteria. All 74 eligible patients were enrolled, of which 37 were allocated to Blanketrol® and 37 were allocated to Rhinochill® therapy.

Exclusions after enrolment: There were four exclusions from patients enrolled: two patients in the Blanketrol® arm and one patient in the Rhinochill® arm were found to have sub-arachnoid haemorrhage on subsequent CT scan following randomisation and one patient in the Rhinochill® arm was already hypothermic (≤34 °C) at randomisation (Fig. 2).

Coronary angiography: Although, all patients were received and enrolled in the cardiac catheter laboratory, four patients allocated to Rhinochill® did not undergo coronary angiography at the physician's discretion (two patients had pre-existing three vessel coronary artery disease, not amenable for PCI and two patients were haemodynamically unstable for catheter laboratory admission). One patient randomised to Blanketrol therapy did not undergo coronary angiography as the admitting physician reported that there was no clear ST elevation on ECG.

Adverse events

There were no trial related adverse events or serious adverse events in patients randomised to Blanketrol®. One patient allocated to Blanketrol® TH induction was withdrawn prematurely due to development of retroperitoneal bleed, unrelated to trial intervention and required surgical intervention equating to 97% success rate of TH device application in this group.

There were four trial related adverse events in patients treated with Rhinochill®—two patients (5.7%) experienced epistaxis and two patients (5.7%) experienced white nose tip. These adverse events recovered without any further intervention upon termination of Rhinochill® induction phase. Four patients randomised to Rhinochill® therapy required early termination of trial intervention and crossed over to Blanketrol® for TH induction and maintenance equating to a success rate of 89% for device employment within the catheter laboratory in this group. Only one of these incidents was trial related: epistaxis ($n = 1$) and the others were unrelated events: acute respiratory distress (pulmonary oedema and peri-arrest gastric aspiration; $n = 2$) and technical difficulties with device ($n = 1$).

There were no exclusions due to withdrawal of consent. All enrolled patients were followed up according to trial protocol. The two groups had similar baseline characteristics prior to randomisation including the mean first temperature recordings (Table 1).

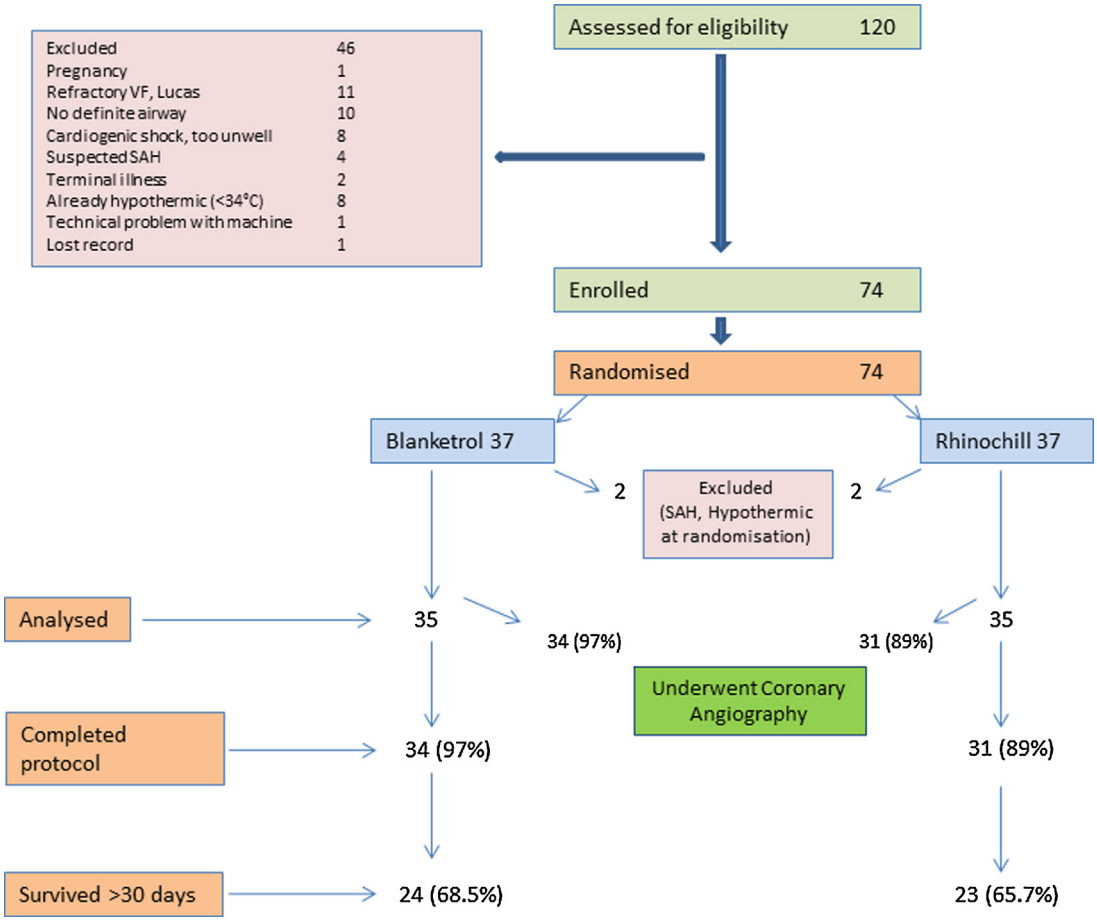

Fig. 2. Flow of participants from recruitment to analysis.

Primary outcomes

TH induction

From randomisation, the mean time to target tympanic temperature (≤34 °C) as a surrogate for brain temperature was 75 min (median 45; range: 0–240) in the Rhinochill® arm in comparison with 107 min in the Blanketrol® arm (median 70; range: 0–366) ($p = 0.101$).

The mean time to oesophageal temperature (≤34 °C) was 85 min (median 50; range 0–270) in the Rhinochill® arm compared with 115 min (median 80; range 10–366) in the Blanketrol® arm from randomisation ($p = 0.151$).

The results are summarised in Table 2 and shown in graphical form in Fig. 3.

Secondary outcomes

In the first hour of cooling, the tympanic temperature dropped significantly more quickly in the Rhinochill® arm than the Blanketrol® arm (1.75 vs. 0.94 °C; $p < 0.001$) (Fig. 3). There were no significant differences between length of ventilation hours, stay in ICU, duration of hospital stay, and CPC one to two outcomes between the two groups (Table 3).

There were no significant differences in survival to hospital discharge between patients treated with Rhinochill® and Blanketrol® therapy (65.7 vs. 68.6%, respectively, Table 3). This equates to a combined survival to hospital discharge of 67.1%.

Discussion

Rhinochill® did not achieve statistical superiority in achieving target temperature (≤34 °C) from randomisation, although there is trend towards faster cooling with Rhinochill® therapy in both tympanic and oesophageal temperature recordings as surrogate for brain temperature and core body temperature, respectively. Rhinochill® induction achieved statistically significant tympanic temperature reductions compared with Blanketrol® during the first hour of cooling suggesting more rapid and focused brain cooling. (Table 3a)

The cooling times in both groups in this trial are impressive when one compares to other trials carried out in this field [2,5,7]. While we have shown that an aggressive cooling strategy in the catheter laboratory can result in a mean time to target tympanic temperature (≤34 °C) of 75 and 85 min with Rhinochill® and Blanketrol®, respectively, there is still a 1–2 h period in the field and during transfer to the HAC where no brain cooling is initiated. It may be that even earlier and even more aggressive targeted brain cooling is required to show a significant survival and neurological improvement when compared with TTM. The PRINCESS trial that is currently recruiting in Europe will help to answer this question, as to whether pre-ROSC-targeted brain cooling can improve cardiac arrest outcomes [23] and if successful, a future large-scale randomised controlled study can be designed to compare intra-arrest cooling and TTM protocol at 36 °C. (Table 3b)

Irrespective of the study intervention, COOLCATH demonstrates a combined survival rate of over 67.1% at hospital discharge in both

Table 2
Temperature data of the two groups: comparison of group means using two-sample permutation *t*-tests and bootstrap 95% confidence limits.

	Blanketrol	Rhinochill	Residual standard deviation
	Mean	Mean	
Outcome measure			
Time to tympanic temp ≤34 °C from randomisation	107.2 (*n* = 32)	75.2 (*n* = 33)	78.4
Time to oesophageal ≤34 °C from randomisation	114.9 (*n* = 33)	84.7 (*n* = 32)	83.4
Tympanic temperature drop (°C in first hour)	0.935 (*n* = 31)	1.75 (*n* = 30)	0.897
Oesophageal temperature drop (°C in first hour)	0.904 (*n* = 24)	1.148 (*n* = 23)	0.573
Tympanic temperature slope (°C in first hour)	-0.808 (*n*= 35)	-1.615 (*n* = 35)	0.867
Oesophageal temperature slope (°C in first hour)	-0.823 (*n* = 35)	-1.21 (*n* = 32)	0.829

groups, which is better than previously reported trials with similar study designs [1,3,13]. Sub-group analysis of patients presenting with initial shockable rhythm demonstrates a combined survival rate was 75.3% which is favourable to previously reported data [7,8]. This could be partly explained by simultaneous coronary intervention and early TH induction in the catheter laboratory, providing maximal myocardial salvage and neuro-protection in these patients. TH has been shown to have beneficial effects on left ventricular myocardial salvage in animal models of coronary artery occlusion and reperfusion [24–26]. Studies of TH in humans presenting with ST elevation myocardial infarction (STEMI) have so far not established significant clinical benefit [27–29]. However, a recent multi-centre randomised controlled trial [27] demonstrated a 33% reduction in infarct size if TH was administered within 4 h of symptom onset in patients with anterior STEMI, and also a reduction in incidence of heart failure was noted in this group. (Table 3c)

Our trial has limitations. In retrospect, the sample size was not sufficient to detect a difference in the primary outcome measure. A

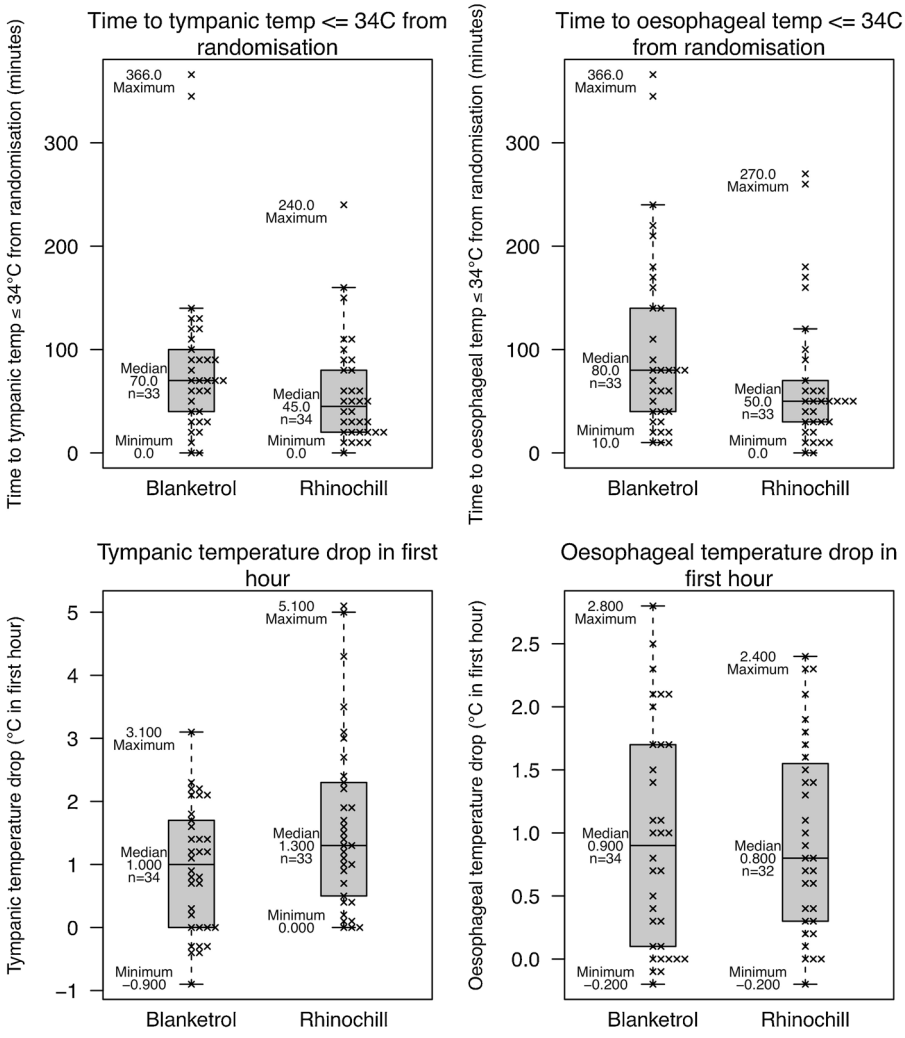

Fig. 3. Medians and ranges of outcome measures for each Study arm limits.

Table 3a
Length of ventilation hours, duration of stay in ICU and hospital: comparison of group means using two-permutation *t*-tests and bootstrap 95% confidence limits.

Outcome measure	Blanketrol mean	Rhinochill mean	Residual standard deviation	Difference:	*p*-value
Length of ventilation (hours)	100.7 ($n = 35$)	218 ($n = 35$)	280.9	117.2	0.079 (-12.3, 254.2)
Length of ICU stay (hours)	145.6 ($n = 34$)	210.5 ($n = 34$)	169.3	64.9	0.122 (-14.5, 142.1)
Length of hospital stay (hours)	447.9 ($n = 35$)	508.9 ($n = 35$)	656.9	61	0.709 (-239.9, 381.9)

Table 3b
Cerebral performance category (CPC): comparison of percentages using Fisher's Exact Test.

Outcome category	Blanketrol	Rhinochill	Difference: Rhinochill – Blanketrol (95% confidence limits)	*p*-value
CPC (1-2) at ICU discharge	51.40% (18/35)	45.70% (16/35)	-5.7 (-27.5, 16.9)	0.811
CPC (1-2) at hospital discharge	57.10%(20/35)	54.30%(19/35)	-2.9 (-24.8, 19.5)	1

Table 3c
Comparison of survival to hospital discharge between two groups.

	Blanketrol	Rhinochill	Overall
Survival to hospital discharge	68.60% (24/35)	65.70% 23/35	67.10% (47/70)

post hoc calculation would suggest that a minimum of 192 patients would be required to have 80% power to detect a statistically significant difference in the time to reach ≤34 °C from randomisation. Secondly, TH was only initiated when the patients were admitted to hospital but ROSC was usually achieved at the site of cardiac arrest. Therefore, valuable time is lost during patient transfer, when no TH is offered to patients, and neurological damage is inflicted. Thirdly, tympanic temperature recordings were taken as a surrogate marker of brain temperature. Whilst earlier studies reported a close correlation between tympanic temperature recordings and brain temperature [30], other studies have challenged this concept [31]. Magnetic resonance spectroscopy [32] and other novel methods of measuring brain temperature can be explored in future trials. Fourthly, the nature of the intervention used meant that the trial was unblinded to some of the treating medical team, which may introduce some bias. Finally, patients were followed up to hospital discharge, which may not give us adequate information regarding neurological recovery and mortality following a cardiac arrest.

Conclusions

Rhinochill® can be applied safely in the cardiac catheter laboratory for the vast majority of patients undergoing emergency PCI following cardiac arrest and during transfer to ICU. The combination of aggressive catheter laboratory cooling and urgent coronary revascularisation in a specialist cardiac unit resulted in a mean overall trial survival rate to hospital discharge of 67.1%. In this study population, Rhinochill® did not achieve better efficiency in TH induction compared with Blanketrol® surface cooling and there were no differences in clinical outcomes between the two groups. There is, however, a non-significant trend in favour of Rhinochill® that potentially warrants further investigation with a larger trial. If such a trial was to show a statistically significant advantage, then future research would be required to determine whether earlier and more rapid targeted brain hypothermia induction improves neurological outcome and mortality in patients presenting with cardiac arrest.

Conflicts of interest statement

Rhinochill® equipment and monitoring support were provided by Benechill GmbH.

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We would like to acknowledge all members of the cardiac catheter laboratory, the ward medical team and the ICU staff at the Essex CTC, who kindly accommodated the trial in this busy tertiary unit. Special gratitude is conveyed to the research office for providing logistic support.

Appendix A. Appendix

A.1. Patient Selection Criteria

Patient Inclusion Criteria

1) ≥ 18 years old
2) Post cardiac arrest with ROSC
3) Planning to receive therapeutic hypothermia as part of post-cardiac arrest care

Patient Exclusion Criteria

1) Cardiac arrest caused by trauma, head injury, massive haemorrhage, drug overdose, cerebrovascular accident, drowning, electric shock or hanging.
2) Already hypothermic (<34 °C).
3) Nasal obstruction preventing the insertion of a nasal catheter.
4) Patients without established definitive airway.
5) Do Not Attempt to Resuscitate (DNAR) orders.
6) Known terminal illness (e.g. malignancy in the end stages).
7) Known or obvious pregnancy.
8) Known coagulation disorder (except those induced by medication, e.g. thrombolytics).
9) Known O_2- dependency.

A.2. CPC Scale

CPC Scale	Interpretation
1	Good cerebral performance or minor disability
2	Moderate disability
3	Severe disability
4	Coma or vegetative state
5	Brain death

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